yet another step in the evolution of what might be called the *nouvelle* health care for patients—and others for that matter. It is becoming clear that both the profession and the public are now coming to view physicians and patients as more or less equal partners in patient care.

This sharing of responsibility with patients should improve results in patient care by improving communication and a patient's understanding of what needs to be done and what may be expected. This is all to the good. It is particularly likely to be true of better educated patients who genuinely wish to understand their health problems and the purpose and use of the medicines prescribed. But these are not all the patients seen by physicians. One cannot help wondering if this principle always holds true if a patient is apprehensive, fearful, not well educated or perhaps even distrustful of the whole health care system because of cultural beliefs or some other reasons. This "nouvelle approach" to health care, particularly when it bypasses the physician in the care of a patient, poses many challenges and also provides many opportunities for conscientious and caring physicians who strive to match the art and science of medicine to the particular needs of each patient.

MSMW

Cardiotoxic Effects of Anthracyclines

ELSEWHERE IN THIS ISSUE, Saltiel and McGuire review the topic of anthracycline cardiotoxicity, a new and totally iatrogenic disease that has generated considerable interest in recent years. The reasons for this interest are several and include (1) the perceived clinical importance of anthracycline cardiotoxicity, a devastating adverse effect of this most useful and promising class of chemotherapeutic agents, (2) the unique quality of cardiotoxic reaction as a side effect of a chemotherapeutic agent and (3) the fascinating complexity of the mechanism(s) of action of the anthracyclines. I will discuss each of these features from my own point of view, and comment on the positions outlined in the review.

As discussed by Saltiel and McGuire, heart failure from dose-related cardiomyopathy is the most clinically important form of anthracycline cardiotoxic effect. This diffuse form of biventricular heart muscle disease is usually a devastating illness that, as first pointed out by Benjamin,[1] is a disease worse than any form of cancer. Almost every practicing oncologist has encountered such a case, and this experience inculcates a healthy respect for anthracycline cardiotoxicity. The imprint of this experience is such that fear of anthracycline cardiotoxicity may lead to underuse of doxorubicin (Adriamycin), the most important single chemotherapeutic agent available to oncologists. Such concern, however, need not limit the use of anthracyclines, any more than fear of marrow suppression limits the use of anticancer drugs. The idea is to learn as much about the problem as possible, and use these drugs in such a way as to minimize the risk of cardiotoxic reaction.

As outlined by Saltiel and McGuire, there are excellent noninvasive and invasive methods for cardiac monitoring during the administration of anthracyclines. Our own recommendations on how to use them[2-4] differ somewhat from those of Saltiel and McGuire in that we do not recommend cardiac monitoring of patients who do not have "risk factors" of previous cardiac radiation, age more than 70 years, previous anthracyclines to a total dose of more than 450 mg per sq m or underlying heart disease including a history of hypertension. In nonrisk patients the extremely low incidence (less than 2%) of heart failure does not justify the cost of cardiac monitoring.[3] For risk-factor patients we recommend either serial radionuclide ejection fractions done at rest and with exercise and with biopsy-catheterization evaluation of abnormal values,[2-4] or biopsy and catheterization only.[3] We[3-5] and others[6] have found that endomyocardial biopsy with morphologic grading according to the Billingham method,[3-6] combined with right heart catheterization, is quite reliable in making dosing recommendations.

The second reason for widespread interest in this subject is the uniqueness of anthracycline cardiotoxicity. Although a few other chemotherapeutic agents have shown "idiosyncratic" cardiotoxicity[7,8] or cardiac toxicity at ultrahigh doses,[9] no other class of agents causes an inexorable dose-related cardiac toxic effect in the manner of the anthracyclines. Sensitivity to the drug varies among individual patients[10] or animals,[11,12] but in each subject a progressive amount of cardiac damages will develop as more drug is given.[10] From a cardiologic standpoint, this process amounts to an extremely useful model of diffuse heart muscle disease, as in a matter of months a cardiomyopathy is created de novo.

Several aspects of this model of diffuse heart muscle disease have practical significance. In patients with cardiotoxic effects of anthracyclines, symptoms of heart failure appear to develop suddenly, and subclinical cardiac dysfunction also develops quite rapidly.[10,13] In uncomplicated cases significant dysfunction occurs when 20% to 25% of heart cells become involved.[10,13] This "nonlinear" form of structure-function relationship means that to be 100% sensitive, noninvasive measurements of cardiac function will have to be done quite often in order to detect the sudden functional deterioration that may result in heart failure. In "Adriamycin equivalents" this interval is every 60 to 120 mg per sq m, or every one to two doses. But because the dose-morphologic damage relationship is linear,[10] when endomyocardial biopsy is the means used to guide therapy this test need not be done as often, as "confidence intervals" of 100 to 200 mg per sq m can be given.[3] Moreover, as noted by Saltiel and McGuire, endomyocardial biopsy is the only method of detecting anthracycline effect at doses below the level at which cardiac function deteriorates. Biopsy is therefore the method of choice for evaluating analogues in phase II trials wherein doses may not be large enough to alter function. Morphologic monitoring, however, must use

glutaraldehyde-fixed specimens and electron microscopy, as routine light microscopy is not adequate for detecting anthracycline effect.[14]

A final point that has led to widespread interest in this topic is the complexity of the mechanism of action of this class of agents. The diverse cellular and subcellular effects of these compounds are such that it is difficult to give a complete review of the subject, and some potentially important actions of anthracycline are not included in the Saltiel and McGuire paper. Anthracycline antibiotics intercalate with DNA and inhibit DNA and RNA synthesis,[15] promote the synthesis of free radicals,[16,17] inhibit the mitochondrial respiratory chain enzyme ubiquinone,[18] alter calcium flux,[19-22] bind to and alter the physical properties of contractile proteins,[23] alter cell surface properties[24,25] including membrane fluidity,[25,26] inhibit guanylate cyclase[27] and are a potent stimulus for the release of vasoactive or cardioactive hormones from heart and other tissues.[12,28,29] This cornucopia of effects insures that the anthracyclines offer something for everybody's favorite tumoricidal or cardiotoxic hypothesis. Because of this pharmacologic complexity, the wisest approach to the study of anthracyclines would probably be to ban them from one's laboratory. For those of us who do not possess such intelligence, it is important to keep certain things in mind:

- Anthracyclines are cytotoxic drugs that affect a wide variety of systems (see below). Accordingly, other cytotoxic agents should always be studied as "controls" before properties unique to the anthracyclines are claimed. For cardiotoxicity, the most appropriate cytotoxic control is probably actinomycin D, which intercalates with DNA with similar affinity[30] and has cell-surface-perturbating properties,[31] but does not possess dose-related cardiotoxicity.

- Because peak plasma levels rarely exceed 1 μg per ml when the drug is given by conventional methods[32-34] and because tissue concentrations are in the range of 1 to 5 μg per gram at periods of maximum uptake,[12,35] it is unlikely that effects of doxorubicin or daunorubicin at concentrations of more than 10^{-5} mol per liter have any pharmacologic meaning. Accordingly, only in vitro studies that examine effects of micromolar concentrations of anthracyclines should receive any serious attention. Indeed, because of their multiple modes of action and general cytotoxic effect, a cellular process not affected by concentrations of doxorubicin of more than 10^{-5} mol per liter would probably be reportable.

- Multiple lines of evidence point to effects on the cell membrane as being crucial to the tumoricidal and cardiotoxic actions of the anthracyclines. A doxorubicin-agarose conjugate that does not enter the cell retains full tumoricidal properties in L1210 cells,[36] and effects of doxorubicin on membrane fluidity can be correlated with relative cytotoxicity.[26] From the point of view of cardiac cells, the sarcolemma plays an extremely important regulatory role and perturbations in it may be expected to promote cellular damage.[37] Evidence that anthracyclines exert a major effect on the sarcolemma include their effects on membrane fluidity in other cells,[24-26] calcium flux,[20-22] guanylate cyclase[27] and release of vasoactive or cardioactive substances.[12,28,29] The effect of anthracyclines on intact cell membranes or on isolated membrane preparations is therefore likely to be a fertile area for future studies.

- In intact tissue anthracyclines may not act by a single mechanism, or at least not exclusively by the mechanism being investigated. There are ample data to suggest that both the tumoricidal properties and the cardiotoxicity of anthracyclines are multifactorial processes, and more attention should be given to interactive mechanisms. For example, antitumor effects may potentially involve the property of DNA intercalation,[15] cell surface properties,[24,26] stimulation of free radical synthesis[15,16] or even release of vasoactive substances.[38,39] Such multifactorial mechanisms of action may create the potential for "combination chemotherapy" within a single agent—one possible explanation for the extraordinary efficacy of this class of compounds.

There is also evidence that multifactorial processes may extend to the mechanism of cardiotoxicity, in that partial but not total protection against cardiac damage may be produced by interference with a number of putative pathogenetic mechanisms. Some of these include prevention of free radical formation,[40,41] administration of coenzyme Q_{10}[42-44] blockade of the effects of or inhibition of the release of cardiac histamine and catecholamines,[12,29] blockade of transsarcolemmal calcium flux[45] and reduction of peak plasma levels by dose-schedule modification.[6] The characteristic quality of the myocardial lesion produced by the anthracyclines[5] does not necessarily argue for a simple, singular cytotoxic site of action, but rather may be better explained by a unique interactive process involving more than one of the proposed cardiotoxic mechanisms. For example, interactive cellular mechanisms of cardiotoxicity might include alteration of the cell membrane and effects on cell surface receptors, including calcium channels; release of cardioactive substances would "summate" with anthracyclines at this locus, producing a cytotoxic increase in calcium flux. At the same time inhibition of cyclic guanosine monophosphate (GMP) synthesis might amplify adenosine 3′:5′-cyclic phosphate (cAMP)-mediated effects of anthracyclines and cardioactive hormones, stimulation of free radical synthesis would increase the membrane perturbation and inhibition of coenzyme Q_{10} would increase the sensitivity to calcium overload-mediated mitochondrial injury. Finally, inhibition of protein synthesis would then impede repair of cell damage. It should be remembered that cells are not isolated enzyme systems, nuclei or membrane preparations, but instead are the delicate interplay of a multitude of processes. In that sense the simultaneous study of multiple isolated systems or the study of intact cells or tissue may yield

more realistic results than the investigation of single, isolated systems.

Because of these complexities, continued study of the tumoricidal effects or mechanisms of drug resistance of this extraordinary class of compounds is certain to provide information of general significance in the field of cancer chemotherapy, just as the study of cardiotoxic mechanisms will continue to provide clues to the pathogenesis of other types of heart muscle disease. For these reasons and because of the paramount importance of the anthracyclines in cancer chemotherapy, we should continue to vigorously investigate the mechanism of action of these compounds with an open mind toward the ultimate conclusions.

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REFERENCES

1. Benjamin RS: Adriamycin dosage schedules and cumulative dose consideration in adults. Presented at the 1st Oncology-Cardiology Workshop on Adriamycin Cardiotoxicity, Dayton, Ohio, 1975

2. Bristow MR: Rational system for cardiac monitoring in patients receiving anthracyclines. Am Soc Clin Oncol Abstr 1980, 356

3. Bristow MR, Lopez MB, Mason JW, et al: Efficacy and cost of cardiac monitoring in patients receiving doxorubicin. Cancer 1982 Jul; 50:32-41

4. McKillop JH, Bristow MR, Goris ML, et al: Sensitivity and specificity of radionuclide ejection fractions in doxorubicin cardiotoxicity. Am Heart J, in press

5. Billingham ME, Mason JW, Bristow MR, et al: Anthracycline cardiomyopathy monitored by morphologic changes. Cancer Treat Rep 1978 Jun; 62:865-872

6. Legha SS, Benjamin RS, Mackay B, et al: Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. Ann Intern Med 1982 Feb; 96:133-139

7. Pottage A, Holt S, Ludgate S, et al: Fluorouracil cardiotoxicity. Br Med J 1978 Mar; 1:547

8. Sanani S, Spaulding MB, Masud ARZ, et al: 5-FU cardiotoxicity. Cancer Treat Rep 1981 Nov-Dec; 65:1123-1125

9. Appelbaum FR, Strauchen JA, Graw RG Jr, et al: Acute lethal carditis caused by high-dose combination chemotherapy—A unique clinical and pathological entity. Lancet 1976 Jan; 1:58-62

10. Bristow MR, Mason JW, Billingham ME, et al: Dose-effect and structure-function relationships in doxorubicin cardiomyopathy. Am Heart J 1981 Oct; 102:709-718

11. Jaenke RS: Delayed and progressive myocardial lesions after Adriamycin administration in the rabbit. Can Res 1976 Aug; 36:2958-2966

12. Bristow MR, Minobe WA, Billingham ME, et al: Anthracycline-associated cardiac and renal damage in rabbits—Evidence for mediation by vasoactive substances. Lab Invest 1981 Aug; 45:157-168

13. Kantrowitz NE, Bristow MR: The structure-function relationship in heart muscle disease. Primary Cardiology, in press

14. Isner JM, Ferrans VJ, Cohen SR, et al: Clinical and morphologic cardiac findings after anthracycline chemotherapy—Analysis of 64 patients studied at necropsy. Am J Cardiol 1983 Apr; 51:1167-1174

15. Zunino F, Gambetta R, Di Marco A: The inhibition in vitro of DNA polymerase and RNA polymerases by Daunomycin and Adriamycin. Biochem Pharmacol 1975 Jan; 24:309-311

16. Handa K, Sato S: Generation of free radicals of quinone group-containing anti-cancer chemicals in NADPH-microsome system as evidenced by initiation of sulfite oxidation. Gann 1975 Feb; 66:43-47

17. Bachur NR, Gordon SL, Gee MV: Anthracycline antibiotic augmentation of microsomal electron transport and free radical formation. Mol Pharmacol 1977 Sep; 13:901-910

18. Iwamoto Y, Hansen IL, Porter TH, et al: Inhibition of coenzyme Q_{10}-enzymes, succinoxidase and NADH-oxidase, by Adriamycin and other quinones having antitumor activity. Biochem Biophys Res Commun 1974 Jun; 58:633-638

19. Anghileri LJ: Ca^{2+}-transport inhibition by the antitumor agents Adriamycin and Daunomycin. Arzneim Forsch/Drug Res 1977; 27: 1177-1180

20. Villani F, Piccinini F, Merelli P, et al: Influence of Adriamycin on calcium exchangeability in cardiac muscle and its modification by ouabain. Biochem Pharmacol 1978 Mar; 27:985-987

21. Azuma J, Sperelakis N, Hasegawa H, et al: Adriamycin cardiotoxicity: Possible pathogenic mechanisms. J Mol Cell Cardiol 1981 Apr; 13:381-397

22. Caroni P, Villani F, Carafoli E: The cardiotoxic antibiotic doxorubicin inhibits the NA^+/Ca^{2+} exchange of dog heart sarcolemmal vesicles. FEBS Lett 1981 Aug; 130:184-186

23. Lewis W, Kleinerman J, Puszkin S: Interaction of Adriamycin in vitro with cardiac myofibrillar proteins. Circ Res 1982 Apr; 50:547-553

24. Murphree SA, Cunningham LS, Hwang KM, et al: Effects of Adriamycin on surface properties of sarcoma 180 ascites cells. Biochem Pharmacol 1976 May; 25:1227-1231

25. Murphree SA, Tritton TR, Smith PL, et al: Adriamycin-induced changes in the surface membrane of sarcoma 180 ascites cells. Biochim Biophys Acta 1981 Dec; 649:317-324

26. Siegfried JA, Kennedy KA, Sartorelli AC, et al: The role of membranes in the mechanism of action of the antineoplastic agent Adriamycin. J Biol Chem 1983 Jan; 258:339-343

27. Levey GS, Levey BA, Ruiz E, et al: Selective inhibition of rat and human cardiac guanylate cyclase in vitro by doxorubicin (Adriamycin): Possible link to anthracycline cardiotoxicity. J Mol Cell Cardiol 1979 Jun; 11:591-599

28. Bristow MR, Sageman WS, Scott RH, et al: Acute and chronic cardiovascular effects of doxorubicin in the dog: The cardiovascular pharmacology of drug-induced histamine release. J Cardiovasc Pharmacol 1980 Sep-Oct; 2:487-515

29. Bristow MR, Kantrowitz NE, Harrison WD, et al: Mediation of subacute anthracycline cardiotoxicity in rabbits by cardiac histamine release. J Cardiovasc Pharmacol, in press

30. Henry DW: Adriamycin, *In* Sartorelli AC (Ed): American Chemical Society Symposium Series, No. 30, Cancer Chemotherapy. Washington, DC, American Chemical Society, 1976, p 15

31. Fico RM, Chen TK, Canellakis ES: Bifunctional intercalators: Relationship of antitumor activity of diacridines to the cell membrane. Science 1977 Oct 7; 198:53-56

32. Benjamin RS, Riggs CE Jr, Bachur NR: Pharmacokinetics and metabolism of Adriamycin in man. Clin Pharmacol Ther 1973 Jul-Aug; 14:592-600

33. Bachur NR, Riggs CE Jr, Green MR, et al: Plasma Adriamycin and daunorubicin levels by fluorescence and radioimmunoassay. Clin Pharmacol Ther 1977 Jan; 21:70-77

34. Benjamin RS, Riggs CE Jr, Bachur NR: Plasma pharmacokinetics of Adriamycin and its metabolites in humans with normal hepatic and renal function. Cancer Res 1977 May; 37:1416-1420

35. Bachur NR, Hildebrand RC, Jaenke RS: Adriamycin and daunorubicin disposition in the rabbit. J Pharmacol Exp Ther 1974 Nov; 191: 331-340

36. Tritton TR, Yee G: The anticancer agent Adriamycin can be actively cytotoxic without entering cells. Science 1982 Jul; 217:248-250

37. Huettner I: The sarcolemma, chap 1, *In* Bristow MR (Ed): Drug-Induced Heart Disease. Amsterdam, Biomedical Press, 1980, p 3

38. Burtin C, Scheinmann P, Salomon JC, et al: The influence of intraperitoneal injections of histamine on tumor growth in fibrosarcoma-bearing mice. Cancer Lett 1981 Apr; 12:195-201

39. Burtin C, Scheinmann P, Salomon JC, et al: Increased tissue histamine in tumour-bearing mice and rats. Br J Cancer 1981 May; 43: 684-688

40. Myers CE, McGuire WP, Liss RH, et al: Adriamycin: The role of lipid peroxidation in cardiac toxicity and tumor response. Science 1977 Jul 8; 197:165-167

41. Doroshow JH, Locker GY, Ifrim I, et al: Prevention of doxorubicin cardiac toxicity in the mouse by N-acetylcysteine. J Clin Invest 1981 Oct; 68:1053-1064

42. Bertazzoli C, Ghione M: Adriamycin associated cardiotoxicity: Research on prevention with coenzyme Q. Pharmacol Res Commun 1977 Mar; 9:235-250

43. Sawada H, Tashima M, Domae N, et al: Chronic cardiotoxicity of Adriamycin and the possible prevention by coenzyme Q_{10} in rabbits. Nippon Gan Chiryo Gakkai Shi 1979 Apr; 14:143-151

44. Bristow MR: Protection against doxorubicin cardiomyopathy in rabbits by coenzyme Q_{10}: Evidence for non-specific myocardial preservation, *In* Yamamura Y, Folkers K, Ito Y (Eds): Biomedical and Clinical Aspects of Coenzyme Q, Vol. 2. Amsterdam, Biomedical Press, 1980, p 179

45. Bristow MR: Anthracycline cardiotoxicity. *In* Bristow MR (Ed): Drug-Induced Heart Disease. Amsterdam, Biomedical Press, 1980, pp 203-206